Diffusion-weighted magnetic resonance imaging at ultra-high field

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Valorisation

Knowledge valorisation: the process of creating value from knowledge, by making knowledge suitable and/or available for social (and/or economic) use and by making knowledge suitable for translation into competitive products, services, processes and new commercial activities. From *Regulations governing the attainment of doctoral degree*, 22, Maastricht University, NL.

8.1 Research

The main goal of this methodological thesis was to present optimised magnetic resonance imaging (MRI) sequences (steady-state free precession, SSFP; and predominantly stimulated echo acquisition method, STEAM) for ex vivo and in vivo quantitative MRI (qMRI) and diffusion-weighted MRI (dMRI) studies in ultra-high field scanners (UHF, from 7 T and above). The advantages of STEAM, severely constrained due to hardware limitations (e.g. B_1^+ inhomogeneity) and sequence drawbacks (e.g. time-expensive), were overcome. It resulted in ultra-high resolution whole-brain dMRI data for ex vivo studies (achieving 400 μm isotropic resolution) using k_T-dSTEAM, and very highly accelerated qMRI and dMRI acquisition protocols for in vivo studies (up to x 54 times the current total acceleration with STEAM; or up to 9 times faster than multiband-only accelerated acquisition) using MESMERISED. With the current feasibility of acquiring ultra-high resolution data and highly sampled multi-contrast MRI images, data-expensive signal models can be employed (e.g. for dMRI, like AxCaliber [12] or ActiveAx [70]) and tractography analysis can benefit; but above all, the biological microstructure features in the brain can be easily more revealed from the resulted analysis [159].

8.2 Relevance

From a scientific point of view, the optimisation of MR sequences was achieved to enable whole human brain acquisitions (either for ex vivo or in vivo studies). These MR images can provide information regarding the entire white matter network systems, the entire grey matter areas connected through these systems, as well the underlying biological microstructure. The concept of visualising biological structures and functions through MRI is defined in the MR community as *in vivo MR histology* (see the review of

Bridge et al. 2006 [37]). This information, which could previously be accessible only through post mortem histology, would help to understand the function and structure of the normal brain but also in diseased brains. For example, as broadly discussed in this thesis, high resolution and multi-contrast imaging could support sophisticated quantitative and diffusion microstructure modelling, such as axon diameter modelling and quantitative myelin modelling. Those models (and others) are relevant to understand brain connectivity in normal brain, and how those biological properties are affected in patients with neuro-degenerative diseases like Parkinson [130], Multiple Sclerosis [195] and Epilepsy [229].
From a clinical point of view, on the other hand, time is a valuable parameter given the restriction of scanning human subjects, especially in diseased conditions. In other words, a proper diagnosis (or clinical application) requires an accelerated version of an often lengthy scientific acquisition protocol: acquire enough data to be analysed with sophisticated (mostly data expensive) models, such that the results enable a robust interpretation. Which can be simplified to *get as much (good quality) data as possible in the shortest time*. Here is where MESMERISED can contribute immensely to this endeavour. In its current state, a full qMRI and dMRI protocol (with included calibration) with MESMERISED can be achieved in 10 to 20 min (at 1.8 mm isotropic resolution) at a 7 T MR scanner (an lighly updated version of which has been FDA approved and CE-marked for clinical use), with promising updates for reducing this time even further without compromising data quality, and a potential to extend its implementation to much more commonly used 3 T clinical scanners.

8.3 Target group

Acquiring MR images with these sequences can be interesting to several groups, because the data type and quality required for *improving pre-processing methods*, *refining analysis models* and *overcoming current software and model limitations* will be accessible. For example, high resolution ex vivo data is computer expensive when the available software for image reconstruction, pre-processing and analysis (especially tractography) are used. Then, software developers can improve their software by using this kind of data[1]. MR physicists and Neuroscientists can use this data to study the validity of signal modelling and compare it with information from his-

[1]This request was already asked for some software developers during the presentation of the k_T-dSTEAM abstract in ISMRM 2018 in Paris, France.

tology, even more if the specimen used is the same. In other words, this can contribute in the aim of in vivo MR histology.
As previously mentioned for the clinical setup, radiologists (or medical physicists) and physicians can experiment with a higher amount of data offered by the MESMERISED sequence. This could help them to estimate how much data and at which resolution *would be necessary for a robust analysis or diagnosis*. This step is really important because a proper diagnosis can help in the prognosis of the patient.

8.4 Activity

All the studies presented in this work are available for the scientific community in the format of poster presentation, power pitch, scientific sessions in international conferences like the International Society of Magnetic Resonance in Medicine (ISMRM) and its corresponding Benelux Chapter (ISMRM Benelux Chapter), the European Society of Magnetic Resonance in Medicine and Biology (ESMRMB) and the Organisation of the Human Brain Mapping (OHBM). Moreover, some of them are published papers with open access (see the references [88] and [87]). Furthermore, the advances in high resolution dMRI of ex vivo human brain tissue have been actively disseminated to the local Maastricht University Medical Centre researchers. The k_T-dSTEAM sequence is a crucial enabling tool in several studies investigating mechanisms and treatments of diseases, such as Epilepsy, Alzheimer's disease, and Parkinson's disease.
The MESMERISED sequence has been patented[2] to protect the intellectual property inherent to its inventive aspects, and ensure that some benefits from commercialising the technology will flow back to scientific research and academic teaching. As of this writing, the patent has been licensed to one major scanner vendor. Complementary to this, Maastricht University and the inventors commit themselves to make all aspects of MESMERISED available without cost to researchers and clinicians for the purpose of non-commercial research, investigation and teaching. This can allow them to implement it in their respective (research and clinical) centres and expand the advantages of this sequence for research studies as well for clinical studies (as mentioned previously).

[2]Inventors A. Roebroeck, B. Poser and F. J. Fritz; CPT and USA patents are pending.